REMARKS

Claims 1 – 43 are pending. Claims 9, 18, and 29 were previously withdrawn. Thus, claims 1 – 8, 10 – 17, 19 – 28, and 30 – 43 are currently under examination. Claims 1-3, 6-8, 10-12, 15-17, 19, 21-23, 26-28, and 31-41 remain rejected, and Claims 42-43 are newly rejected, under 35 U.S.C. §103(a) as allegedly unpatentable over WO 03/004599 A2 to Peleg et al. ("Peleg") in view of the journal publications of Matsuda et al. ("Matsuda"), or Ishii et al. ("Ishii"), or Kim et al. ("Kim"), as maintained in the previous Office Action. Claims 4, 5, 13, 14, 24, and 25 also remain rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Peleg in view of Matsuda, Ishii, or Kim, and further in view of WO 01/057217 to Kwon et al. ("Kwon"). Claims 16, 27, 42, and 43 are newly rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claim 43 is newly rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. Finally, Claim 10 is objected to as allegedly grammatically incorrect.

All rejections and objections are respectfully traversed. Reconsideration and favorable action are requested in light of the foregoing amendments and the following remarks.

Claim 10 is amended to correct the alleged grammatical error and to more particularly point out and distinctly define the claimed subject matter. Claim 43 is amended to more particularly point out and distinctly define the claimed subject matter. The claim amendments herein are intended put the claims in better form for consideration for Appeal. Applicants respectfully request entry of the present amendments into the record, in accordance with 37 CFR 1.116(b)(2) and MPEP 714.12, despite the amendments being made after a Final Rejection, since the required Notice of Appeal is being filed herewith . No new matter is added into the case by the amendments.

Finally, Applicants would like to thank the Examiner for the correct withdrawal of the previous rejection of Claim 20.

A. Claims 1-3, 6-8, 10-12, 15-17, 19-23, 26-28, and 30-43 Patentably Distinguish Over The Cited References.

Claim 1 is directed to an expression vector which comprises, among other things, a polynucleotide which encodes a fusion protein. The fusion protein includes a signal sequence of the gac gene of *Pseudomonas diminuta* (hereinafter "*P. diminuta*") and a polypeptide of interest,

other than the polypeptide encoded by the gac gene of *P. diminuta*. The signal sequence and the polypeptide of interest are linked in such a way that, upon expression of the polynucleotide as a fusion protein in a suitable host cell, the signal sequence is cleaved from the fusion protein and the polypeptide of interest is released into the periplasm of the host cell. Claim 10 is directed to a prokaryotic host cell which, among other things, is stably transformed with the claimed expression vector. Claim 20 is directed to a process for making a polypeptide using such a prokaryotic host cell transformed using such an expression vector, in accordance with claim 10. Claims 42 and 43, respectively, are independent claims directed to a prokaryotic host cell transformed with an expression vector which is compatible with the host cell, as described above, and a process for production of a polypeptide of interest, also as previously described.

In an effort to show that Applicants' claims would have been considered obvious, the Examiner has assembled various combinations of parts of four distinct references. The primary reference, Peleg, with which the other references are combined, does not teach, disclose, or suggest an expression vector that comprises a polynucleotide sequence that codes for a fusion protein which includes the claimed signal sequence of the gac gene of *P. diminuta*.

Peleg deals with making a fusion polypeptide by introducing an expression construct containing a viral-derived TAT signal peptide. Cited in combination with Peleg are Matsuda, Ishii, and Kim. However, Matsuda, Ishii, and Kim are not directed toward production of a polypeptide of interest, other than the gac gene of *P. diminuta*, as specifically called for in the claims. Rather, they pertain to various disparate genetic and molecular biological characterizations of the gac gene in some species of *Pseudomonas*, and of the expression of gac protein in *E. coli*. Nothing in these references reveals any motivation or suggestion to modify Peleg to make a fusion protein marrying two polynucleotides as called for in the claims.

Despite the above and other deficiencies in the assembled references, the Examiner maintains in a conclusory fashion in response to the Applicants' previous arguments that it would have allegedly been obvious to use the gac signal sequence said to be described in Matsuda, Ishii, and/or Kim as a substitution for the virally-derived TAT signal sequence of Peleg in an expression vector in order to produce a polypeptide of interest according to Applicants' claims.

However, the mere mention of the gac gene signal sequence in Matsuda, Ishii, or Kim cannot be said to motivate a person of skill to reconfigure Peleg to make Applicants' invention as claimed. Applicants do not claim (nor could they) to have invented the gac gene. Furthermore,

there is no suggestion in this group of references to make Applicants' invention employing a fusion protein that includes a signal sequence of the gac gene of *P. diminuta*, and in some claimed embodiments, the promoter and/or ribosomal binding site of the same gac gene, and a polypeptide of interest other than the gac gene of *P. diminuta*, all linked in such a way in the fusion protein so as to cause the latter to be released into the periplasm of the host cell upon expression of the polynucleotide in the host cell.

A primary reason the alleged combination would not have been obvious under the law is that it seems to be based on an assumption that it is at least presumed obvious to make any combination that can be broken down into known parts. The examiner literally says in conclusory fashion that this combination would have been "obvious to try" in light of the combined references (page 5, Final Action). It seems that the entire basis for the rejection rests on the statement that there are a "finite number of signal sequences available in the art". No support is provided for this statement other than the allegation that the parts needed for the combination existed before, somewhere in some form. This cannot lawfully serve to preclude patentability under U.S. law in fields of art where there is little to no predictability (See *Abbot Laboratories v. Sandoz Inc.*, U.S. Court of Appeals of the Federal Circuit, 544 F3d 1341, 89 USPQ2d 1161).

Nothing in the art of record suggests making the claimed expression system and fusion protein, or predicts that the claimed system and protein would be successful. This knowledge has been gleaned by the Examiner from the Applicants' disclosure, and used against the Applicants to search for art that a person of ordinary skill in the art at the time the invention was made would necessarily not have had any reason to seek. This point may be further driven home in light of the primary reference, Peleg, which provides a perfectly reasonable lead signal sequence (i.e., the virally-derived TAT sequence disclosed therein) for the investigation of other recombinant expression systems. Thus, any researcher reading Peleg would likely select virally-derived TAT signal peptides as options for experimentation that might lead to expected successes.

Even though the number of known signal peptides across all domains of life is finite, so is the number of atoms in the universe. Yet that does not preclude the patentability of every new composition of matter as obvious. Furthermore, new signal peptides are still being discovered by scientists, therefore the number of known signal peptides is always increasing. By the Examiner's reasoning, the obviousness rejection made in this case would also apply to every new

combination of signal peptide and protein of interest in any expression system. The Examiner seems to be saying that it would be obvious to try any signal peptide in any expression system for secretion of a protein of interest. Such reasoning does not provide lawful basis for an obviousness rejection, especially in light of the teachings of the Supreme Court in *KSR v. Teleflex* (82 USPQ2d 1385).

According to *KSR v. Teleflex* (id.) the so-called "obvious to try" basis for finding obviousness was only said to be applicable with regard to a finite number of identified, predictable solutions to a particular problem, when there is an outside pressure in the direction of the solution. The decision was NOT made with regard to an alleged finite range of different biological sequences that might be used to construct an otherwise novel fusion protein. It is not even germane to the matter at hand that there "might" be some X thousand or ten thousand or million number of "signal peptides" any more than it would be to a patent on a novel steel bridge structure with unique properties that there might be X million pieces of steel of various lengths, etc. While certain mechanical inventions may properly be rejected as obvious to try, under the guidance from *Abbot Laboratories v. Sandoz Inc.* (id.), the present subject matter may not.

Here, it is not reasonable to suppose as "obvious" that every known signal sequence will work with every peptide in every expression system imaginable, including in the claimed fusion protein system, as the Office Action seems to suggest and it is clear beyond peradventure that at least an undue amount of experimentation, serendipity, and/or other inventive activity would certainly be required for a researcher attempting to arrive at the present claims based solely on the cited references, *without first having foreknowledge of the Applicants' disclosure*. Such a rejection amounts to impermissible hindsight reasoning, and should be withdrawn.

It is well accepted in the art, that while many genetic recombinations "might" be useful, the science of genetic engineering as a whole is quite unpredictable, and is known to be so by persons of ordinary skill. Without at least a concomitant reasonable expectation of success and some pre-existing reason in the art to make this specific substitution, it is not lawful to erect this as an alleged obvious combination under Section 103. The examiner has pointed to no pre-existing knowledge or information in the art as to why a person would have any reasonable expectation for success in substituting the gac signal sequence as claimed by Applicants into an expression vector according to the process of Peleg. Without such information, the invention cannot lawfully be said to be obvious. In point of fact, the art seems to lead away from the very thing the examiner alleges would have been "obvious" to do. Ishii teaches that "the signal

sequence is foreign to *E. coli* and not effectively recognized by *E. coli* signal peptidase" (page 596, last paragraph). Accordingly, the combined disclosure of Ishii and Peleg would actually have served to discourage a person of ordinary skill in the art who read these references from attempting to make any sort of combination and would, if anything, have discouraged from working in the direction of Applicants' invention.

Even if a person having ordinary skill in the art was thinking about the gac signal sequence along the lines of Applicants' invention while reading Peleg, and there is no reason why they would, there is no lawful basis to say it would have been obvious for such a person to engage in speculative "cutting and pasting", or substitution, of the gac signal sequence in exchange for the virally-derived signal sequence of Peleg, since the latter is the main thrust of Peleg. There is no basis in any analogous teaching to motivate one to believe the system described by Peleg would be compatible with Applicants' claimed gac signal sequence. Nothing has been said in any of the cited references to suggest that a substitution of Peleg's virally-derived sequence with Applicants' claimed gac signal sequence in the expression vector of Peleg would be desirable, or even operable, for releasing a polypeptide of interest into a cell periplasm of a host cell in the manner claimed by the Applicants.

Just for the sake of argument, a person of ordinary skill in the art reading Peleg should already be aware of the existence of signal sequences and their functions in regards to cellular protein production. This same hypothetical person would also be aware that there are a great many known signal sequences across all domains of life. Additionally, this same person would perhaps also have the common knowledge that not every signal sequence will work in every desired expression system, and certainly that different signal peptides may provide unpredictable performance advantages in the expression of some proteins over other proteins in recombinant expression systems. Some other variables that may be known to a person of ordinary skill in the art to affect protein expression are the organism used for the expression system, the culture conditions under which the organism is grown, and the expression vector itself.

Thus, this hypothetical person reading Peleg would have understood the teachings of Peleg point to the use of a viral TAT derived signal peptide as a starting point for further experimentation. Yet, according to the Examiner, out of the multitude of known signal peptides (over 27000, according to the Signal Peptide Database maintained at http://proline.bic.nus.edu.sg/spdb/index.html), this hypothetical person would have immediately thought of and made the substitution of the claimed gac signal sequence of *P. diminuta* from the

viral TAT signal peptide of Peleg, even though there is not any teaching, suggestion, or motivation to do so from within Peleg, or any of the cited references. This is a clear case of unlawful and impermissible hindsight reasoning, and Applicants respectfully urge the Examiner reconsider the claims and withdraw the rejection.

In other words, there would be no reason for a person of ordinary skill in the art to even seek out references related to the gac signal sequence of *P. diminuta* based on reading Peleg alone. Nothing about Peleg suggests resorting to the other references, or *vice-versa*. Therefore, as described above, the hypothetical person using Peleg as a starting point for experimentation would be more likely apply Peleg in an effort to try other virally derived signaling systems similar to those described by Peleg, rather than bacterial signal sequences such as the one claimed, or any other signal sequences other than viral sequences.

The only mention in Peleg of *Pseudomonas* is as part of a list of bacteria that could be suitable for use with Peleg's claimed expression system. There is absolutely no indication from Peleg that *Pseudomonas* should be investigated for signal peptides useful in recombinant fusion proteins desired to be expressed in a host call's periplasm. It is well established that motivation for combining references cannot come from the Applicants' disclosure, which is certainly the case here, as shown above.

Therefore, it would not even arguably be obvious to try the claimed signal sequence of the gag gene from *P. diminuta* without some suggestion or motivation from Peleg that this particular signal peptide would work in the claimed system. Even if there were some suggestion in the prior art that the *P. diminuta* gac signal would be effective in targeting some polypeptides from a fusion protein for secretion in some expression systems, the fact remains that the art as a whole is entirely unpredictable, and there is no way of even supposing that a signal peptide will have the desired effect or efficiency in every possible expression system, including the claimed one.

Furthermore, there is an even more insurmountable degree of unpredictability when components from across domains of life are intermingled in a single expression system, for example, in a recombinant expression system where the signal peptide may come from a prokaryotic organism, the desired POI is from non-prokaryotic organism, and the expression system uses a prokaryotic organism (which need not be the same prokaryotic organism that the signal peptide was derived from). Some signal peptides (SP's) are incompatible with some POI's,

and some SP and POI combinations are not efficient or even operable in some expression systems.

Accordingly, for at least the above reasons, the Examiner's logic for asserting that the *Pseudomonas* gac signal sequence would have been obvious to try in the claimed expression system is untenable, and with all due respect, the rejection should be withdrawn.

Applicants most earnestly urge the examiner to acknowledge the fact that even if a person of ordinary skill in the art managed to somehow collect the cited references together and consider them all at once (and there is zero reason for him to do so), there is no known or cited motivation or suggestion for combining the references in the manner imagined because the references are so utterly divergent in their teachings that it cannot be argued that it would have been obvious to combine them in the proposed manner. As stated above, the only way to arrive at the present claims from considering the cited references is through impermissible hindsight after having learned of Applicants' disclosure. No suggestion of Applicants' claims is found from an objective consideration of these references in accordance with how they are to be viewed under the law. Accordingly, independent claims 1, 10, 20, 42 and 43 patentably distinguish over the references assembled by the Examiner.

Claims 2-3 and 6-8 depend from claim 1, claims 11-12, 15-17, and 19 depend from claim 10, and claims 21-23, 26-28, and 30-41 depend from claim 20. The dependent claims add further elements and limitations to the base claims, also not found in the references. According to the MPEP, if a base claim is patentable relative to the cited art, then all claims dependent thereon are also patentable over the same art. Since independent claims 1, 10, 20, 42 and 43 have been shown to patentably distinguish over the prior art, all claims dependent thereon should also be allowed. Hence, reconsideration and allowance of claims 1-3, 6-8, 10-12, 15-17, 19-23, 26-28, and 30-43 are respectfully requested.

B. Claims 4, 5, 13, 14, 24, and 25 are Patentably Distinct Over the Cited References.

Claims 4, 5, 13, 14, 24, and 25 are dependent claims rejected as allegedly obvious from Peleg combined with Matsuda, Ishii, or Kim, and further combined with Kwon. However, there is, in the first place, no lawful or valid basis to suppose that one of skill in the art would assemble and then attempt to combine isolated parts of Peleg, Matsuda, Ishii, and Kim in an effort to arrive at the claimed invention, , as described in part B above. But, even if there was some reason or motivation to combine parts of these references as imagined, and there is not, there is still no

further teaching, suggestion, or disclosure within Kwon or otherwise that would have led one of skill in the art to make the invention of the subject claims. Kwon is directed toward the expression, in *E. coli*, of a heterologous fusion protein comprising a polypeptide of interest and an *E. coli* heat stable enterotoxin II signal sequence. Once again, Applicants do not claim to have invented the concept of recombinant "fusion protein." But nothing about Kwon's disclosure of a special fusion protein including *E. coli* would have suggested a fusion protein as claimed by Applicants containing a signal sequence for the gac gene and a polypeptide of interest that, upon expression of the polynucleotide, causes a cleavage of the gac signal sequence and release of the polypeptide of interest into the cell periplasm. No indication is given in Kwon that any signal sequence other than that of the highly specific *E. coli* heat stable enterotoxin II (such as the *P. diminuta*-derived signal sequence of the present claims) would be of any use in a fusion protein expression system for producing a polypeptide of interest according to Applicants' claims. The mere fact that Kwon discloses hIFNα-2a and hIFNα-2b as a polypeptide of interest in one expression system says nothing about the performance of those proteins in other expression systems, or makes any suggestion as to what, if any, alternative expression system might be suitable, certainly nothing along the lines of Applicants' expression system.

Accordingly, a person of ordinary skill in the art reading Peleg, Matsuda, Ishii, Kim, together with Kwon (and there is no readily apparent reason why any person of ordinary still would choose these particular references out of the thousands of others and then attempt to somehow combine them in an effort to make Applicants' claimed invention for genetic manipulations, without first having knowledge of the Applicants' disclosure), would have no "obvious" reason to reconfigure isolated fragments of the references and then try to combine them in the manner imagined by the Examiner to arrive at the present claims.

In fact, the only conceivable reason for any person to collect and reconfigure these references in the manner of the Office Action would be as part of an effort to construct Applicants' claims from hits and pieces of the prior art, using the invention itself as the blueprint. This is impermissible now, just as much as it was pre-KSR. Such practice follows neither the law nor the MPEP. Accordingly, reconsideration and allowance of claims 4, 5, 12, 14, 24, and 25 are respectfully urged.

C. Claims 16, 27, 42, and 43 Are Not Indefinite.

From the text of the Office Action, it appears as though the Examiner may have misunderstood Applicants' recitation of a "second" polynucleotide. The word "second" was included merely to clarify that the expression vector could comprise an additional polynucleotide sequence, different from the previously recited polynucleotide sequence that includes the promoter sequence and the ribosomal binding site (RBS) from the gac gene of *P. diminuta*. The specification is clear on this point, as described on pages 6-8. The term "second" was only intended to differentiate between the parts of the expression vector, which in one embodiment combines polynucleotide sequences for the gac promoter, the gac RBS, the gac signaling sequence, and a polypeptide of interest (other than gac) in a single expression vector, which in all embodiments are operably linked to the gac promoter, the only promoter discussed in relation to the claimed expression system. Accordingly, since the claims must be read and interpreted in light of the teachings of the specification, the claims are not indefinite and the reconsideration and allowance of Claims 16, 27, 42, and 43 are respectfully requested.

D. Claim 43 Does Not Contain New Matter.

Claim 43 does not contain new matter for the same reason that Claims 16, 27, 42, and 43 are not indefinite, discussed in part C above. However, Applicants have amended the claim to more particularly point out and distinctly define the claimed subject matter. Accordingly, reconsideration and allowance of Claim 43 are hereby respectfully requested.

E. The Objection to Claim 10.

Claim 10 is objected to as allegedly being grammatically incorrect. The claim is amended to clarify and more particularly point out and distinctly define the claimed subject matter. Accordingly, Applicants believe the Objection to Claim 10 to be moot in light of the present amendment. Reconsideration and withdrawal of the Objection to Claim 10 are hereby respectfully requested.

CONCLUSION

Applicants assert that the specification and claims of the present application meet the requirements of 35 U.S.C. §§112, 102, and 103, and are patentably distinguished from the prior art made of record. Applicants respectfully submit that a full and complete response to the office

action is provided herein, and that the application is now fully in condition for allowance. Action in accordance therewith is respectfully requested.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. 122355.

Respectfully submitted,

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